Tinnitus and hyperacusis in children: clinic reports and basic research

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Abstract Objective Tinnitus and hyperacusis are subjective symptoms which can be reported by people of any age. Although tinnitus and hyperacusis can have a negative effect on child development, these symptoms are commonly overlooked by their parents and clinicians. In this paper, we review clinical reports on tinnitus and hyperacusis in children and basic scientific studies on these disorders in order to provide updates of these disorders in the pediatric population. Recent studies have found that tinnitus and hyperacusis are not uncommon in children, especially in those with conductive and sensorineural hearing loss. The parents and clinicians should pay attention when children show abnormal behaviors and especially when they develop hearing loss. Since there is no objective measurement for tinnitus and hyperacusis, the diagnosis in children can be challenging. Tinnitus and hyperacusis are also common in Williams syndrome and autism but the mechanisms are still not clear. High doses of salicylate and noise exposure can induce tinnitus. Animal studies have determined lack of inhibition in the auditory cortex and the inferior colliculus may be critical for tinnitus and hyperacusis generation. The non-classic auditory system may also be involved in the awareness and tolerance of tinnitus and hyperacusis.

Key words tinnitus; hyperacusis; auditory system; salicylate; acoustic trauma

Tinnitus, defined as any sound sensation unrelated to external acoustic or electrical signals [1], is a common disease in otolaryngological clinics. Tinnitus is an annoying and debilitating disorder that can affect the quality of people's life. Tinnitus patients sometimes are not only bothered in quiet environment, but also by an ordinary environmental sound which is perceived as extremely loud and uncomfortable, known as hyperacusis [2]. Tinnitus and hyperacusis can be coexisting symptoms of excessive auditory perception in general population, especially in adults. In the last decade, there has been a rapid increase of studies on tinnitus treatment and research.

Although tinnitus and hyperacusis in children have been reported, the symptoms have not received adequate attention from most of clinicians. This may be partially because children do not know how to complain or they are not bothered by these symptoms. Most children can easily ignore tinnitus if they are playing or doing various things [3]. However, children can be affected by a noisy sound [4], which negatively affects their learning and social interactions. Recent studies have reported that tinnitus and hyperacusis are common symptoms in other known disorders, such as Williams syndrome, autism, hearing loss, etc. Therefore, we have reviewed clinical reports on tinnitus and hyperacusis in children in order to provide updates on these symptoms in the pediatric population in this paper. We also have reviewed current research on tinnitus and hyperacusis in order to find potential clues for tinnitus and hyperacusis treatment.

Tinnitus and hyperacusis in Williams syndrome

Williams syndrome is induced by large duplicated deletions on the long arm of chromosome (7q11.23) (Hillier et al., 2003). Children with Williams syndrome often show various physical and developmental delays, including pixie facial features – flat nasal bridge, broad forehead

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and wide mouth with prominent lips [5]. Hyperacusis is a very common symptom in children with Williams syndrome. The prevalence of hyperacusis in Williams syndrome reaches almost 94% [6]. A survey of 78 children with Williams syndrome found that the sensory modulation impairment played an important role in hyperacusis. Children with Williams syndrome showed serious sensory modulation disorders, including poor adaptive and executive functioning, with increased behaviors and temperaments problems [7]. A study found that subjects with Williams syndrome had high-frequency sensorineural hearing loss in pure-tone audiograms and distortion products of otoacoustic emission (DPOAE) tests (Gothelf et al., 2006). Otitis media was also reported in children with Williams syndrome. A survey among 65 individuals with Williams syndrome found that 95% presented with hyperacusis and 61% with otitis media [8]. However, the correlation between the degree of hyperacusis and the frequency of otitis media in Williams syndrome has not been identified [9].

Tinnitus and hyperacusis in autism

Autism is a neural developmental disorder characterized by impaired social interaction and poor communicative skills. Autistic children have trouble to link words to their meanings and have difficulties to communicate with other kids. Children with autism also have abnormal responses to auditory stimuli. Hyperacusis is common, affecting 18% of the autism group based on a study among 199 children with autistic disorders [10]. Hyperacusis has been identified as one of the symptoms in autism since the first autism case was reported. Autism patients have sensory gating deficits which may be related to the impaired inhibitory interneuron function and the imbalance of the excitatory and inhibitory nervous systems [11]. Studies suggest that some forms of autism may be caused by increased ratio of excitation/inhibition in sensory, memory and emotional systems [12]. About 30% of autistic children develop apparent seizures and have ongoing sharp spike activity in EEG during sleep. These results suggest that the hyperexcitable cortical and subcortical states may mediate language and social behaviors, including the striking hypersensitivity to auditory and tactile stimuli [13].

Hearing loss relates to tinnitus and hyperacusis

Hearing loss is one of the risk factors associated with tinnitus [14]. In a study based on hearing screening and interviews in 756 healthy 7-year-old school children, 41% reported having experienced tinnitus in some form, 17% of these children reported recurrent temporary threshold shifts and 7% had more than 20 dB permanent hearing loss. The probability of spontaneous tinnitus was 27% for children with no hearing loss, but 63% if they exhibited either temporary or permanent hearing loss. This study confirmed an increased occurrence of spontaneous tinnitus in children with hearing loss. A study involving 1037 subjects found children who had otitis media and a raised audiometric threshold were more likely to experience tinnitus in adulthood [15]. A study of the prevalence of tinnitus in children found that chemotherapy and radiotherapy may also cause tinnitus or sensorineural hearing loss (Whelan et al., 2011). This study found that cancer patients were more likely to develop hearing loss and tinnitus, since the chemotherapy medicine and radiation induced toxicity of the outer or inner hair cell of the cochlea. Tinnitus caused by such therapies is likely related with damage in the auditory system (Whelan et al., 2011). Other diseases related to tinnitus, such as Fabry disease (Keilmann et al., 2009) , head trauma [16] and superior semicircular canal dehiscence (Lee et al., 2011), are associated with hearing loss. In addition, tinnitus has also been reported in children without any other detectable otologic problems [17]. However, whether cochlear damage is not detected or not present in these children is still in debate.

Basis research of tinnitus and hyperacusis

While cochlear injuries cause a reduced activity in the auditory nerve, the neural activity in the central auditory system seems to increase [18]. The increased activity in the central auditory system may amplify neural noise due to the overall increase of gain and ultimately causes tinnitus [19]. In the clinic, hyperacusis is considered as a pre-tinnitus symptom and the two often occur together [20]. Tinnitus is related to increased discharge along the auditory pathways, including cochlear nucleus, inferior colliculus and auditory cortex [21]. In some cases tinnitus may be due to increased spontaneous discharges in these areas [20].

Some studies suggest that in addition to the classical auditory system, non-classical systems, including hippocampus, amygdale and somatosensory system, may also

be involved in tinnitus and hyperacusis (De Ridder et al., 2006; Hwang et al., 2009). It has been reported that extralemniscal auditory system neurons, which is critical for generating auditory information, can receive signals from the somatosensory system. Some researchers suggest that maturation process of the non-classical auditory pathways is delayed in children with tinnitus or hyperacusis (Moller et al., 2002). As the brain in children is more plastic than adults and it can be influenced by environment factors such as the noise exposure and high-risk activities [22].

Salicylate and acoustic trauma have been used to induce tinnitus in animal models [23]. High doses of salicylate can induce reversible tinnitus and hearing loss (Cazals, 2000). It is reported that high doses of salicylate can reduce cochlear output, but virtually increase sound evoked auditory cortex response [24]. Salicylate also causes exaggerated acoustic startle response, suggesting an increased sound reaction, a sign of hyperacusis behavior (Sun et al., 2009a; Yang et al., 2007). These results suggest that effects of salicylate are on both the peripheral and central auditory systems. In vitro studies suggest that salicylate can reduce GABAergic inhibition in the central nervous system, including the inferior colliculus, the auditory cortex and the hippocampus (Gong et al., 2008; Sun et al., 2009b). Wang et al detected that salicylate could attenuate inhibitory postsynaptic currents in the auditory cortex and the inferior colliculus, suggesting that the alteration of inhibitory neural circuits may be one of the cellular mechanisms for tinnitus induced by salicylate (Wang et al., 2006; Wang et al., 2008). Salicylate induced enhancement of auditory response in the auditory cortex can be blocked by balcofen, a GABA-B receptor agonist [25].

Noise exposure can also cause enhanced cortical response [26]. The increased cortical response is not likely caused by the peripheral damage, as the cochlear output is reduced. Wang et al. found that acute noise exposure impaired side-band inhibition in inferior colliculus neurons which could result in enhanced firing rates and widened tuning curves [27]. Ben Scholl reported that acute acoustic trauma could also induce imbalance of the excitation and inhibition in auditory cortical neurons [28]. They found that noise trauma induced synaptic inhibition was decreased at low frequencies but enhanced at high frequencies after noise exposure. This study indicates that acoustic trauma may cause an asymmetrical damage on inhibitory field in auditory cortex [28]. These changes happen very rapidly (within less than an hour) which are likely caused by direct damage of the inhibitory neurons. Our recent study indicates that acute noise trauma can enhance acoustic startle response, suggesting that damage of the inhibitory system may cause greater sound reaction [29]. Therefore, salicylate and noise trauma may cause tinnitus and hyperacusis through affecting the inhibitory circuitry in the central auditory system.

Early age hearing loss can significantly impair the central auditory system development. It has been reported that early age conductive hearing loss and sensorineural hearing loss during the critical period of development, can induce audiogenic seizure – loud sound causes seizure behavior (Chen, 1978; Henry, 1972). Recently, our lab found that tympanic membrane damage at postnatal 16-35 days induced a long lasting audiogenic seizure on rats even after hearing loss totally recovered. Interestingly, the rats with tympanic membrane damage also showed increased acoustic startle response, suggesting an increased sensitivity to acoustic stimulation [30]. This indicates that conductive hearing loss at early age may be related with hyperacusis reported in children with recurrent otitis media [14]. However, more studies are needed to reveal the connection between audiogenic seizure and tinnitus and hyperacusis.

Clinical implication of these findings

It is important to identify children suffering from tinnitus or hyperacusis, because tinnitus in children can induce a significant impact on their life. It is difficult to diagnose tinnitus or hyperacusis among children. The reason is that tinnitus is a subjective symptom and it is difficult for children to answer questionnaires accurately. These often lead to an under-estimation of the occurrence of tinnitus in children. Thus, the research on children with tinnitus should also include questionnaires for their parents, direct interview, ear-related inspection, and audiometric tests (air conduction audiometry, tympanometry and contralateral acoustic reflex threshold, etc.) [22]. Sometimes, tinnitus may accompany other symptoms, such as hearing loss, headache, dizziness or irregular behavior.

In summary, tinnitus and hyperacusis in children have not drawn attention in most of clinicians. The mechanisms and risk factors associated with tinnitus are still

not clear. The objective of this review is to summarize the limited literatures in this area and alert the professionals of the high incidence of tinnitus and hyperacusis in children. Therefore, the clinician can advise parents on avoiding their children's exposure to risk factors associated with tinnitus and hyperacusis such as loud noise and ototoxic drugs; and pursuing timely treatment of otitis media, etc. The basic research on tinnitus and hyperacusis focusing on the changes of the central auditory system, including both classical and non-classical pathways, may help develop improved treatment for tinnitus and hyperacusis.

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